UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

April 7, 2003

MEMORANDUM

SUBJECT: **MGK® Repellent 326 (Di-N-propyl isocinchomeronate)** HED Risk Assessment for Reregistration Eligibility Document (RED) PC Code No: 047201; DP Barcode: D289139

FROM: Becky Daiss, Environmental Health Scientist
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Attached is the Health Effects Division (HED's) human health risk assessment conducted in support of the Reregistration Eligibility Document (RED) for use of MGK® Repellent 326 (Di-N-propyl isocinchomeronate) as a human and animal pest repellent. This document revises the January, 2003 version to address technical correction comments submitted by the registrant. The disciplinary science chapters and other supporting documents have also been revised to address technical correction comments. They are included as appendices as follows:

Report of the Hazard Identification Assessment Review Committee. A. Khasawinah (TXR No. 0051423, 12/20/02)
Product Chemistry Chapter. J. Stokes (D285966, 11/26/02)

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21.0 EXECUTIVE SUMMARY

The five phase data submission and review process required under the 1988 Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) has been completed for MGK® Repellent 326. The purpose of this document is to provide an assessment of risks associated with the existing pesticidal uses of MGK® Repellent 326 in support of the reregistration eligibility decision, and to determine whether infants and children exhibit enhanced sensitivity from exposure to MGK® Repellent 326.

Use Profile

MGK® Repellent 326 (dipropyl-isocinchomeronate) is an insect repellent registered for inclusion in personal use products that are applied topically to humans, and in health care products for pets (i.e., dogs, cats, and horses). Repellents are thought to work by confusing the insects so they can't locate the target host. MGK® Repellent 326 is never used as a sole active ingredient in either personal use or pet repellants. It is always combined with another repellent and/or insecticide in addition to solvents, propellants and other inert ingredients. In insect repellent formulations used for human application, MGK® Repellent 326 is always combined with N,N-diethyl-m-toluamide (DEET). Formulations intended for animal application may contain piperonyl butoxide, pyrethrins, and DEET. MGK® Repellent 326 is used to repel flies, gnats, and similar pest insects and is used in combination with other repellents which are used to repel other types of insects (e.g., mosquitos, ticks, etc.).

MGK-326 is used mostly in pressurized sprays, i.e., aerosol canister products. It can also be formulated in lotions, towelettes, gels, sticks, creams, and pump sprays. MGK® Repellent 326 is primarily used in animal health products such as sprays for dogs, cats and horses. Animal products represent more than 60% of total U.S. sales. Human personal use products account for approximately 40% of U.S. sales. During the year 2002, 24,702 pounds of a.i. were produced and sold, of which 38% was sold to customers with pesticide labels for use as "personal insect repellents," 54% for use on horses, and 8% for use on dogs and cats (Use Closure Memo, T. Spears, 1/17/03). Syndicated market data for 1990 show that the most commonly used human personal use insect repellents containing DEET are aerosols (71.9%), followed by pump sprays (15%), liquids (6%), lotions/creams (1.4%, roll-ons/sticks (0.7%) and towlettes, (0.2%). The amount of MGK® Repellent 326 in currently registered human personal use products ranges from 1 to 4%. The majority (approximately 90%) of human products contain 2.5% or less of the active ingredient (a.i.) MGK® Repellent 326. Amount of MGK® Repellent 326 in animal products ranges from 0.1 to 5% with the majority of products containing 1% or less.

Regulatory History

MGK® Repellent 326 has undergone the five phase process for accelerated registration established by Section 4 of FIFRA. The data submissions and reviews required under FIFRA have been completed. During the reregistration process, McLaughlin Gormley King (MGK) Company, the registrant of the technical grade of the active ingredient, decided not to support livestock or food uses. Accordingly, MGK's Phase 2 response dated August, 24, 1989 included an amendment to revise the label for all of its technical formulation products to include the statement "for use in manufacturing of pesticide products for use in indoor non-food and residential areas only". Additionally, the registrant submitted voluntary cancellation notices for all end use products with livestock and/or food processing uses on the label. Based on these actions by the technical registrant, OPP sent Data Call In (DCI) notices to all end use registrants who used MGK® Repellent 326 for these purposes. The end use registrants were given the option of providing supporting data, amending their labels to include language to prohibit the use of these products on animals to be used as food or feed, or deleting the use on cattle and/or horses entirely. Therefore, reregistration data requirements based on these uses (i.e., residue chemistry) are no longer applicable and HED recommends revocation of tolerances for the following commodities for which uses have been deleted from MGK® Repellent 326 product labels; meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep, and milk. The FIFRA reregistration review also indicated that MGK® Repellent 326 products for use in lakes and ponds are no longer registered. MGK, Inc., also opted to delete outdoor use patterns from its label. Therefore, requirements based on aquatic food and non-food, and outdoor uses are no longer applicable.

The final step in the FIFRA reregistration process is an OPP determination of whether the remaining registered uses of MGK® Repellent 326 are eligible for reregistration or submission of additional studies on product and residue chemistry, and toxicology are required to confirm the reregistration eligibility. The purpose of this risk assessment is to support the reregistration eligibility decision. This assessment also includes a determination of potential enhanced sensitivity of infants and children from exposure to existing uses of MGK® Repellent 326.

Hazard Identification and Dose Response Assessment

The toxicology data base is adequate to characterize the toxicity of MGK® Repellent 326. MGK® Repellent 326 has low acute toxicity via the oral (Toxicity Category III), inhalation (Toxicity Category IV), and dermal (Toxicity Category III) routes of exposure. MGK® Repellent 326 is not a skin irritant (Toxicity Category IV) or eye irritant (Toxicity Category III). It is not a dermal sensitizer.

Toxic effects by MGK® Repellent 326 in experimental animals occur at relatively high doses. Body weight loss is characteristic of chronic exposures. In mice, doses of 500 mg/kg/day in the diet for 18 months caused decreased body weight and body weight gains and increased liver/gall bladder weights in both sexes, and increased liver histiocytosis in males. In rats, doses of 250 mg/kg/day in the diet for two years caused decreases in the absolute and relative kidney weights in males and females. In dogs, dietary doses of 148 mg/kg/day for a year inhibited body weight gain. Higher doses in dogs caused a decrease in the liver and kidney weights, and liver histological changes. Subchronic dietary exposures resulted in decreased body weights at 1000-2000 mg/kg/day. MGK® Repellent 326 did not cause toxic effects after subchronic exposures through inhalation to 0.324 mg/L (60 mg/kg/day) or through dermal application of 100 mg/kg/day for 90 days.

Developmental toxicity occurred at high doses (>1000 mg/kg day in rats; >100 mg/kg/day in rabbits) which were higher than those causing maternal toxicity in rats or rabbits. There were also no indications of teratogenic effects in experimental animals. However there is quantitative and qualitative evidence of increased susceptibility of the offspring during *in utero* exposure to MGK® Repellent 326 in a two generation reproduction study in rats. Decreased body weight of pups was noted at 250 mg/kg/day doses compared to the same effect in the parents occurring at 1000 mg/kg/day. Pup mortality was also noted at the 1000 mg/kg/day dose with no parental mortality occurring at this dose.

High doses in the diet of rats (1000 mg/kg/day) and mice (2000 mg/kg/day) produced increases in the incidence of liver and renal cell tumors in male and female rats, and increased the incidence of liver adenomas in female mice and alveolar bronchiolar adenomas in male mice. These findings were the basis for classifying MGK® Repellent 326 as a B2 carcinogen - probable human carcinogen by HED's CPRC. It should be noted that the carcinogenic effects were seen at the limit dose (rats) or at twice the limit dose (mice) for carcinogenicity testing. Because HED has not received additional data from the registrant to allow for a re-evaluation the cancer classification, HED will not revisit this issue at this time. However, should additional data be submitted in the future, HED may revisit the cancer classification.

MGK® Repellent 326 was tested for bacterial reverse mutation, *in vitro* mammalian cell gene mutation in CHO cells and mouse lymphoma cells and for unscheduled DNA synthesis in rat primary hepatocytes and found negative. Dietary administration of MGK® Repellent 326 at doses reaching 1555 mg/kg/day for 28 days did not produce peroxisomal proliferation, did not induce peroxisomal enzymes or induce cytochrome P-450 microsomal enzymes (MRID 43033301).

The Hazard Identification and Assessment Review Committee (HIARC) concluded that the toxicology database for MGK® Repellent 326 is adequate for FQPA and/or special sensitivity

to children considerations. This committee also concluded that no additional safety factor is required to address traditional uncertainties (e.g., extrapolation from subchronic to chronic endpoints, use of a LOAEL due to lack of a NOAEL, incomplete database, etc). In addition, since MGK Repellent 326 is not registered for use in/on foods and has no supported or proposed new tolerances, the special FQPA safety factor is not applicable to risk assessments for this chemical. Although FQPA does not apply to this risk assessment, HED examined the toxicity and exposure databases to determine if any special concerns for infants and children exist. Based on this examination, HED has determined that this risk assessment is adequately protective of all population subgroups, including infants and children.

The residential exposure scenario is the only relevant scenario for exposure to MGK® Repellent 326. There are no registered uses involving direct application of MGK® Repellent 326 to agricultural crops or to livestock, and no outdoor uses of MGK® Repellent 326. Therefore, toxicological endpoints for dietary and drinking water exposure are not required. Incidental oral and dermal endpoints were selected based on a two generation reproductive rat study. The inhalation endpoint was selected on the basis of a 90 day rat inhalation study. The cancer endpoint was selected based on a combined chronic toxicity/carcinogenicity study in rats and a carcinogenicity study in mice. Residential exposure endpoints used in the risk assessment are provided in Table 1.

Table 1. Endpoints Used for MGK® Repellent 326 Risk Assessment

Exposure Route/Term	NOAEL mg/kg/day	Target MOE
Incidental Oral - Short & Intermediate	65	100
Dermal - Short & Intermediate	65	100
Inhalation - Short & Intermediate	60	100
Cancer	Q_1* = 1.6×10^{-3} mg/kg/day	

Exposure Assessment

Use of MGK® Repellent 326 is limited to direct application to humans and pets (i.e., non-food animals). There are no registered uses involving direct application of MGK-326 to agricultural crops or to livestock. There are no outdoor uses of this product. Therefore, dietary and drinking water exposure assessments were not required. There are no specific occupational uses of MGK® Repellent 326 i.e., MGK® Repellent 326 is typically applied to pets by pet owners on an as needed basis, per label directions – it is not typically applied on a regular basis by professional pet groomers or veterinarians. Therefore, based on current use patterns, only residential exposure pathways were included in the MGK® Repellent 326 risk assessment.

Residential exposure to MGK® Repellent 326 results from direct human application of personal use products and application of animal care products to pets.

Risk Assessment and Risk Characterization

Due to limited use patterns, the risk assessment was conducted for residential exposure pathways only. A cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity has not been conducted for this RED because HED has not yet determined if there are any other chemical substances that have a mechanism of toxicity common with that of MGK® Repellent 326.

Residential Pathway Exposure and Risk

Potential residential scenarios include short term exposures that occur when people apply the product topically to themselves or to pets. This assessment estimated exposure and risk for the following exposure scenarios: dermal exposure from direct application of MGK® Repellent 326 to human skin; potential incidental oral exposure of children from topical application, i.e., potential exposure from incidental hand to mouth contact after repellent is applied to a child's skin, or after transfer of residue from a treated pet to a child's hands, and potential inhalation exposure from use of repellent sprays.

The target Margin of Exposure (MOE) is 100 for all residential routes of exposure. The MOEs estimated for all of the residential exposure scenarios described above showed no risks of concern (i.e. all MOEs were > 100). The Q_1* for the cancer risk estimate is 1.6 $x10^{-3}$ mg/kg/day. The estimated cancer risk for residential exposure to MGK® Repellent 326 is 5 $x10^{-6}$. In general, the Agency is concerned if cancer risk estimates exceed 1 x 10^{-6}. Therefore, MGK® Repellent 326 may present potential cancer risks of concern from residential exposure.

Aggregate Exposures and Risks

Since there is no potential for concurrent exposure via the food, water and residential pathways, an aggregate risk assessment was not conducted.

Data Gaps

All pertinent chemistry data requirements are satisfied except Guideline 830.7050 (UV/Visible Absorption), 830.1700 (Preliminary Analysis), 830.1750 (Certified Limits) and 830.1800 (Enforcement Analytical Method). However, most of the necessary data have been

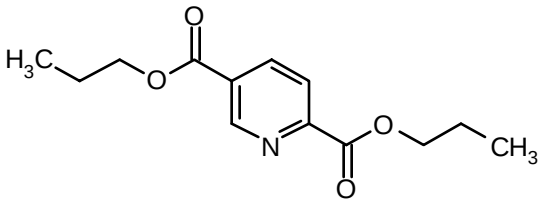
submitted and HED has no objections to the reregistration of MGK® Repellent 326 based on product chemistry requirements, provided that the registrant submits the outstanding data requirements. (D285966, J. Stokes, 11/26/02) There are no gaps in the required toxicological data.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Common Name: dipropyl isocinchomeronate
Chemical Name: dipropyl isocinchomeronate
Trade Names: MGK® Repellent 326
Empirical Formula: $C_{13}H_{17}NO_4$
CAS No.: 136-48-8
PC Code: 047201
Structure:

Molecular Weight: 251.3
Physical State: viscous liquid at room temperature
Color: white/amber
Solubility in Water: 0.892 g/L
Vapor Pressure: 4.92 x 10^{-7} mm Hg at 25 C
Melting Point: NA - liquid at room temperature
Boiling Point: 150 C at 1 mm Hg

Pure MGK® Repellent 326 is an amber liquid. MGK® Repellent 326 is practically insoluble in water. It is miscible with petroleum distillates such as kerosene, toluene, xylene, methanol, ethanol and isopropanol. It is stable under ambient storage conditions and unstable at temperatures above 120 C. The vapor pressure of MGK® Repellent 326 is 5 X 10^{-7} mm Hg at 25 C. The log of the octanol/water partition coefficient ($logP_{ow}$) is 3.567. The dissociation constant for MGK® Repellent 326 is: K_a = 0.119 at 25 C.



3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

The toxicity data base for MGK® Repellent 326 is adequate for the selection of doses and endpoints for use in risk assessment. HED's Hazard Identification Assessment Review Committee (HIARC) evaluated the acceptable studies available in the database and established doses and endpoints for short and intermediate-term incidental oral exposure, and short and intermediate-term dermal and inhalation exposure scenarios. For residential exposures, uncertainty factors (UFs) are used to determine adequate margins of exposure (MOEs). The MOE is the ratio of the route appropriate NOAEL to the estimated exposure. The HIARC also evaluated available studies to determine if there was special sensitivity for infants and children. The toxicological data are summarized in Tables 2 and 3.

3.1.1 Acute Toxicity

MGK® Repellent 326 has low acute toxicity via the oral (Toxicity Category III), inhalation (Toxicity Category IV), and dermal (Toxicity Category III) routes of exposure. MGK® Repellent 326 is not a skin irritant (Toxicity Category IV) or eye irritant (Toxicity Category III). It is not a dermal sensitizer. Acute toxicity categories for MGK® Repellent 326 are shown in Table 2.

Table 2. Acute Toxicity Data on MGK® Repellent 326 (Technical)

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00155068	LD_{50} = 5850 mg/kg, 4270 mg/kg 5120 mg/kg +	III based on female toxicity
81-2	Acute Dermal	41648601	LD_{50} = > 2000 mg/kg	III
81-3	Acute Inhalation	41571501	LC_{50} = > 6.09 mg/L	IV
81-4	Primary Eye Irritation	41800501	not an eye irritant	III
81-5	Primary Skin Irritation	41826505	not a skin irritant	IV
81-6	Dermal Sensitization	41648602	not a skin sensitizer	NA

3.1.2 Toxicity Profile

Table 3 identifies and summarizes guideline studies conducted for MGK® Repellent 326.

Table 3 Toxicity Profile for MGK® Repellent 326.

Chronic Studies			
GL #	MRID	Study Type	Results and Classification
83-5 870.4300	4209390 2 4297350 1	24-Month Combined Chronic/Carcinogenicity Feeding-Rats, Sept. 30, 1991 100% a.i. 0, 0, 65, 250 or 1000 mg/kg/day	**LOAEL** = 250 mg/kg/day based on decreases in the absolute and relative kidney weights in males and females **NOAEL** = 65 mg/kg/day. At 1000 mg/kg/day (upper limit dose), the test compound produced increases in the incidence of liver and renal cell tumors. Body weights, food consumption and food efficiency were significantly decreased in males and females at this dose. **Acceptable/guideline**
83-2b 870.4200b	4210010 2	18-Month Carcinogenicity in Mice, Sept. 30, 1991 100% a.i. 0, 0, 125, 500, or 2000 mg/kg/day (2 x limit dose).	**LOAEL** = 500 mg/kg/day based on decreased body weights and body weight gains in both sexes, increased liver/gall bladder weights in both sexes, and increased liver histiocytosis in males. **NOAEL** = 125 mg/kg/day At 2000 mg/kg/day, the test compound increased incidences of liver adenomas in females and alveolar bronchiolar adenomas in males. **Acceptable/guideline**
83-1b 870.4100	4232060 2	12-Month Chronic Oral Toxicity (dietary) - Dogs September 19, 1989 99.5% a.i. 0, 250, 1,000 or 4,000 ppm (0, 8.27, 34.3, or 148.0 mg/kg/day for males; 0, 8.12, 34.1 or 117.5 mg/kg/day for females) 2-month Range Finding Study: 0, 4,000, 7,500, 15,000/10,000; 30,000/1,000 or 60,000/2,000 ppm	**Main Study** **LOAEL =** 4,000 ppm (148.0 mg/kg/day) based on the inhibition of body weight gain **NOAEL** = 1,000 ppm (34.3) mg/kg/day. **Range Finding Study** At 7500 ppm: marked decrease in body weights and food consumption, a decrease in the liver and kidney weights, liver histological changes (centrilobular hypertrophy, bile duct proliferation and portal fibrosis). At 15,000/10,000 ppm: marked increase in alanine transferase activity in both sexes, a slight decrease in the testicular weights of males and in the ovarian weights of females. **Acceptable/guideline**

Table 3. Toxicity Profile for MGK® Repellent 326			
Sub-chronic Studies			
GL #	MRID	Study Type	Results and Classification
82-1 870.3100	42093901	90-Day Dietary Study in Rat, October 24, 1991 100% a.i. 0, 125, 250, 500, 1000 or 2000 mg/kg/day	**LOAEL** = 1000 mg/kg/day, based on the reduction in body weights in both sexes, and organ weight decreases in males. **NOAEL** = 500 mg/kg/day **Acceptable/Guideline**
82-1 870.3100	42100101	90-Day Dietary Range Finding Toxicity Study - Mice. October 24, 1991 100% 0, 125, 250, 500, 1000, or 2000 mg/kg/day)	**LOAEL** = 2000 mg/kg/day based on decreased body weights and body weight gains and increased food consumption and liver (mild tan foci-multilobular) and kidney (mild white focus-unilateral) effects observed in males. **NOAEL** = 1000 mg/kg/day **Acceptable/Guideline** (when considered with MRID 42100102)
82-4 870-3465	42990201	90-Day Inhalation Toxicity Study - Rat. April 2, 1993. 100% a.i. 0, 0.0105, 0.028, 0.095, or 0.324 mg/L for 6 hours/day, 5 days/week	**LOAEL** = >0.324 mg/L (60 mg/kg/day) for systemic effects based on the lack of toxic effects. **NOAEL** = 0.324 mg/L (60 mg/kg/day). **Acceptable/Guideline**
82-2 870.3200	42427202	90 - Day dermal toxicity - rabbits. July 16, 1992 100% a.i. 0, 10, 30 or 100 mg/kg/day, 6 hours/day, 7 days/week.	**LOAEL** = 100 mg/kg/day for dermal effects based on fissuring and moderate skin reactions and the **NOAEL** is 30 mg/kg/day. **LOAEL** = >100 mg/kg/day for systemic effects based on the lack of toxic effects and the **NOAEL** is 100 mg/kg/day. **Acceptable/Guideline**

Table 3. Toxicity Profile for MGK® Repellent 326			
Developmental Studies			
GL #	MRID	Study Type	Results and Classification

Table 3. Toxicity Profile for MGK® Repellent 326			
Developmental Studies			
83-3a 870.3700	41987802	Developmental Toxicity- Rat: April 6, 1991 100% 0, 100, 300 or 1000 mg/kg/day Range Finding 0, 100, 200, 400, or 800 mg/kg/day	**Maternal Toxicity** **LOAEL** = 1000 mg/kg/day based on reduced body weight gain (14.5% decrease; $p<0.01$) during GD 6-15. **NOAEL** is 300 mg/kg/day. **Developmental Toxicity** **LOAEL** = >1000 mg/kg/day (the highest dose tested; the **NOAEL** is 1000 mg/kg/day **Acceptable/guideline**
Non- Guideline	45682901	Range finding teratology study - Rabbit, August 28, 1986. 100% purity, orally via gavage at 0, 125, 250, 500, 1000 or 2000 mg/kg/day (5 females/group) on gestation days 7 through 19.	Mortality occurred at the 500, 1000, and 2000 mg/kg/day group (60%, 100%, 100%, respectively). The surviving animals were comparable to control animals in behavior and appearance. The mean number of viable fetuses, postimplantation loss, total implantations and corpora lutea of the 125 and 250 mg/kg /day groups were comparable to those of the controls. Doses of 35, 100, and 350 mg/kg/day were selected (MRID 40433301) for developmental toxicity study. This study is **acceptable** for the purpose it was designed for.
83-3b 870.3700	40433301	Developmental Toxicity- Rabbit: Oct. 29, 1987. 100% purity 0, 35, 100, or 350 mg/kg/day	**Maternal Toxicity** **LOAEL** = 350 mg/kg/day, based on mortality preceded by decreased body weight gain. Low incidence of clinical signs: leaning to the left, labored breathing, involuntary eye movement, dry white material in nasal area, decreased motor activity, and no righting reflex. several animals that died or were sacrificed *in extremis* displayed no clinical signs of toxicity. **NOAEL** = 100 mg/kg/day. **Developmental Toxicity** **LOAEL** = was not observed. Due to high mortality in the 350 mg/kg/day does, fetal toxicity at this dose could not be evaluated. No fetal toxicity was observed at 35 or 100 mg/kg/day. **NOAEL** = 100 mg/kg/day. **Acceptable/guideline**

Table 3. Toxicity Profile for MGK® Repellent 326			
Developmental Studies			
83-4 870.3800	41547801	2-Generation reproduction- Rat, June 7, 1990, 100% purity dietary dose levels of 0, 65, 250 or 1000 mg/kg/day	**Parental Toxicity** **LOAEL** = 1000 mg/kg/day based on decreased body weights, body weight gains, and food consumption and histopathological liver changes in the males and females (trace to mild biliary stasis and portal bile duct proliferation in F_0 females. Trace to mild portal bile duct proliferation and trace portal mononuclear cell infiltrates in the F_1 males and females) **NOAEL** = 250 mg/kg/day **Offspring Toxicity** **LOAEL =** 250 mg/kg/day based on decreased pup body weight. At 1000 mg/kg, increased deaths in F_1 pups relative to controls during PND 0-4 and PND 4 through 21 and the F_2 pups during PND 4 through 21 were noted. **NOAEL** = 65 mg/kg/day.**Acceptable/guideline**

Table 3. Toxicity Profile for MGK® Repellent 326			
Metabolism and Absorption Studies			
GL #	MRID	Study Type	Results and Classification
85-1 870-7485	42305701	Metabolism- ADME Study - Rat May 11, 1990 pyridine-4-^{14}C- MGK® Repellent 326 used. 1) single oral 100 mg/kg for blood collection over 14 hour period. 2) single oral 100 **or** 1000 mg/kg/day **or** single iv dose of 1 mg/kg and held 168 h. 3) daily oral dosing 100 mg/kg of unlabeled compound for 14 days followed by a single oral dose of labeled 100 mg/kg and held for 168 h.	Pyridine-4-^{14}C- MGK® Repellent 326, administered orally, was absorbed rapidly and reached a peak blood level at 30 minutes and 45 minutes after dosing in male and female rats, respectively. Its blood halflife was 1.5 hours. About 89 - 99% of the administered dose was eliminated within 12 hours of dosing, mainly in the urine. Fecal excretion was minimal and accounted for 1-3% of the administered dose (occurred after the first 12 hours of dosing). Residual radioactivity in the tissues was nil to insignificant. There were no differences between males and females or between single oral or multiple dosing regarding the elimination pattern of the radioactivity. In the single high dose group, the elimination of the radioactivity appeared to be slower than the other groups. In the iv dosing, the elimination of the radioactivity was much faster; 87- 89% of the administered dose was eliminated during the first 4 hours. The fecal excretion was less than 1.3% of the administered iv dose. **Acceptable/guideline**

Table 3. Toxicity Profile for MGK® Repellent 326			
Metabolism and Absorption Studies			
85-1 870-7485	42246502	Metabolism- Identification of Metabolites - Rat. Addendum to MRID 42305701	HPLC metabolic profiles of male and female rat urine were similar. HPLC analysis revealed a major peak (Metabolite A: 95-99% of the urinary radioactivity) and a minor peak (Unknown 1; up to 4.5%). The parent compound was not detected in the urine samples. Metabolite A fraction was further purified, concentrated and analyzed with mass spectrometry (MS) and identified as the dicarboxylic acid derivative of MGK Repellent 326. Based upon these results, it was postulated that the parent compound was hydrolyzed at the two ester sites to form the dicarboxylic acid derivative of MGK Repellent 326. **Acceptable/guideline**
85-1 870-7485	42246501	Metabolism- determination of expired CO_2 - Rat August 20, 1990. Pyridine-4-^{14}C- MGK® Repellent 326 used. Single oral dose 105 mg/kg	None to a negligible amount (<0.04%) of the ^{14}C in the pyridine ring of the parent compound was metabolized to $^{14}CO_2$. **Acceptable/guideline**

Table 3. Toxicity Profile for MGK® Repellent 326			
Metabolism and Absorption Studies			
Non-Guideline	43099401	Metabolism Study - Humans December 15, 1993 Pyridine-4-^{14}C- MGK® Repellent 326 used 6.1-6.8 mg/kg; 95.1uCi oral 2 adult healthy males	Peak radioactivity blood levels were attained at 2 - 4 hours with a plasma half-life of 5.3-8.0 hours. The test compound was rapidly absorbed from the gastrointestinal system and eliminated in the urine (41.5% - 54% during the first 8 hours; 81.9-85.1% of the AD during the first 36 hours). Total urinary excretion of the radioactivity amounted to 82.3-85.8% of the AD by 128 hours after dosing. Excretion of the radioactivity in the feces was minimal and occurred mostly within the first 6 hours after dosing (1.87% - 2.61% of the AD). The balance of the AD was not accounted for. The HPLC analysis of the 0-24 hour composited urine of the two volunteers revealed three metabolites with no parent compound present. These were identified by mass spectrometric (MS) analysis as the hydrolysis products of the parent material: Metabolite A: the diacid of MGK 326 (39.8% of the urinary radioactivity), Metabolite B ; 5-carboxy unesterified (3.9% of the urinary radioactivity) and Metabolite C: 2-carboxy unesterified (40.3% of the urinary radioactivity). Metabolites B and C were converted to Metabolite A by acid hydrolysis. **Acceptable/non-guideline**
Non-guideline	42974602	Dermal Absorption & Mass Balance- Humans June 18, 1992. Formulated Pyridine-4-^{14}C-MGK® Repellent 326 (1.1% w/w) with DEET (17.5% w/w) and MGK 264 (5% w/w). 46.6 ug/cm^2 in isopropanol. 3 healthy human volunteers.	Plasma radioactivity levels indicated that the formulated ^{14}C-MGK® 326 was continuously absorbed through the human skin, and a peak plasma concentration was reached when the exposure was terminated. Plasma radioactivity levels dipped after isopropanol wash. **Mean dermal absorption of radiolabeled MGK-326 (sum of radioactivity in urine and feces) from an 8 hr exposure was 3.4% (cumulative total measured over 128 hrs)**. Absorbed radioactivity was eliminated mainly in the urine and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropyl alcohol swabs (78%). Mean total recovery of applied dose was 102.17%

Table 3. Toxicity Profile for MGK® Repellent 326			
Metabolism and Absorption Studies			
Non-guideline	42974601	Dermal Absorption & Mass Balance- Humans June 17, 1992. Pyridine-4-^{14}C- MGK® Repellent 326. 41.7 ug/cm^2 in isopropanol 4 healthy human volunteers	Plasma radioactivity levels indicated that ^{14}C-MGK® 326 was steadily absorbed through the human skin, and a peak plasma concentration was reached when the exposure was terminated at 8 hours. **Mean dermal absorption of radiolabeled MGK-326 (sum of radioactivity in urine and feces) from an 8 hr exposure was 24.9% (cumulative total measured over 128 hrs).** Absorbed radioactivity was eliminated mainly in the urine (24.7% of the applied dose) and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropanol wash (48.5%). Mean total recovery of applied dose was 95.5%.
Non-guideline	42732101	Dermal Absorption & Mass Balance: Multiple Dosing - Humans February 25, 1993. Formulated Pyridine-4-^{14}C-MGK® Repellent 326 (1.0% w/w) with DEET (17.5% w/w) and MGK 264 (5% w/w). 4.2 ug/cm^2 daily for 14 days followed by 4.2 ug/cm^2 of the labeled material (37.9 uC) on day 15.	Plasma radioactivity levels indicated that the formulated ^{14}C-MGK® 326 was continuously absorbed through the human skin, and peaked when the exposure was terminated. The plasma radioactivity levels as a function of time were analogous to those obtained with single dose dermal application of the pure material (MRID 42974601) and the formulated material (MRID 42974602). **Mean dermal absorption of radiolabeled MGK-326 (sum of radioactivity in urine and feces) from an 8 hr exposure was 4.75% (cumulative total measured over 128 hrs).** Absorbed radioactivity was eliminated mainly in the urine and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropyl alcohol swabs (79%). Mean total recovery of applied dose was 99.28.

Table 3. Toxicity Profile for MGK® Repellent 326			
Metabolism and Absorption Studies			
85-3 870.7600	42246503	Dermal Absorption - Rats January 20, 1990. Pyridine-4-^{14}C- MGK® Repellent 326. **Group 1**: Five male rats 80 ug/cm^2 in isopropanol. Blood collected over 168 h. **Groups 2-5**: Five males/group 60 ug/cm^2, sacrificed at 1, 10 , 19 or 168 hours.	The test material was absorbed through the skin and rapidly reached a peak blood level (13% of the administered dose) at 1 hour after dosing and gradually declining reaching a plateau level after 24 hours. The study author calculated a first half life of 9 hours and a second half life of 19 hours. **Mean dermal absorption of radiolabeled MGK-326 (the sum of radioactivity in urine (major amount), feces, tissues/carcass, and cage wash) after 10 hours of exposure was 45%.** Mean recoveries of the test material ranged from (95-103%). The majority of recovered test material was found in the skin rinse at the 1 and 10 hr time intervals (86 and 53% respectively). Mean amounts of test substance found in the skin rinse decreased significantly at the 19 and 168 hr time intervals (31 and 7% respectively) indicating that material remaining in/on the skin continues to be absorbed over time.

Table 3. Toxicity Profile for MGK® Repellent 326			
Special Studies			
GL #	MRID	Study Type	Results and Classification
Non-guideline	43033301	Hepatic Enzyme Induction Study - Rats, April 9, 1992 99.7% purity 0, 96.9, 373.4, 783.9 or 1554.5 mg/kg/day for 28 days to males. Positive control: Sodium phenobarbital (PhB: 53.7 mg/kg/day	MGK 326 did not affect serum chemistries. It did not produce peroxisomal proliferation, induce peroxisomal enzymes (palmitoyl-CoA oxidation) or induce cytochrome P450 dependent mixed function oxidase enzymes including *N*-ethylmorphine *N*-demethylase, 7-ethoxycoumarin *O*-deethylase, 7-ethoxyresorufin *O*-deethylase or, amma-glutamyl-transferase. MGK 326 was not a rat liver microsomal enzyme inducer. **Acceptable/non-guideline**

Table 3. Toxicity Profile for MGK® Repellent 326			
Special Studies			
Non-guideline	42974603	Whole Body Autoradiography Study - Rat. March 16, 1992. 99.7% purity Pyridine-4-^{14}C- MGK® Repellent 326, 100 mg/kg body weight	Only xeroxed copies of the original autoradiograms were submitted in the report and were difficult to evaluate due to their poor quality. No quantitative data on the distribution of the radioactivity in the various tissues and body regions were presented in the report. **Unacceptable/Non-Guideline**. This type of study was not required.

3.1.3 Hazard Characterization

The toxicology data base is adequate to characterize the toxicity of MGK® Repellent 326. MGK® Repellent 326 has low acute toxicity via the oral (Toxicity Category III), inhalation (Toxicity Category IV), and dermal (Toxicity Category III) routes of exposure. MGK® Repellent 326 is not a skin irritant (Toxicity Category IV) or eye irritant (Toxicity Category III). It is not a dermal sensitizer.

Toxic effects by MGK® Repellent 326 in experimental animals occur at relatively high doses. Body weight loss is characteristic of chronic exposures. In mice, doses of 500 mg/kg/day in the diet for 18 months caused decreased body weight and body weight gains and increased liver /gall bladder weights in both sexes and increased liver histocytosis in males. In rats, doses of 250 mg/kg/day in the diet for two years caused decreases in the absolute and relative kidney weights in males and females. In dogs, dietary doses of 148 mg/kg/day for a year inhibited body weight gain. Higher doses in dogs caused a decrease in the liver and kidney weights, liver histological changes (centrilobular hypertrophy, bile duct proliferation and portal fibrosis). Subchronic dietary exposures resulted in decreased body weights at 1000-2000 mg/kg/day. MGK® Repellent 326 did not cause toxic effects after subchronic exposures through inhalation to 0.324 mg/L (60 mg/kg/day) or through dermal application of 100 mg/kg/day for 90 days.

Developmental toxicity occurred at high doses (>1000 mg/kg day in rats; >100 mg/kg/day in rabbits) which were higher than those causing maternal toxicity in rats or rabbits. There were no indications of teratogenic effects in experimental animals. However there is quantitative and qualitative evidence of increased susceptibility of the offspring during in utero exposure to MGK® Repellent 326 in a two generation reproduction study in rats. Decreased body weight of pups was noted at 250 mg/kg/day doses compared to the same effect in the parents occurring at

1000 mg/kg/day. Pup mortality was also noted at the 1000 mg/kg/day dose with no parental mortality occurring at this dose.

High doses in the diet of rats (1000 mg/kg/day) and mice (2000 mg/kg/day) produced increases in the incidence of liver and renal cell tumors in male and female rats and increased the incidence of liver adenomas in female mice and alveolar bronchiolar adenomas in males. These findings were the basis for classifying MGK® Repellent 326 as a B2 carcinogen - probable human carcinogen by HED CPRC. It should be noted that the carcinogenic effects were seen at the limit dose (rats) or at twice the limit dose (Mice) for carcinogenicity testing. Because HED has not received additional data from the registrant to allow for a re-evaluation the cancer classification, HED will not revisit this issue at this time. However, should additional data be submitted in the future, HED may revisit the cancer classification.

MGK® Repellent 326 was tested for bacterial reverse mutation, in vitro mammalian cell gene mutation in CHO cells and mouse lymphoma cells and for unscheduled DNA synthesis in rat primary hepatocytes and found negative. Dietary administration of MGK® Repellent 326 at doses reaching 1555 mg/kg/day for 28 days did not produce peroxisomal proliferation, did not induce peroxisomal enzymes or induce cytochrome P-450 microsomal enzymes (MRID 43033301).

3.2 FQPA Considerations

3.2.1 Traditional Additional Uncertainty Factors (Addressing Data Deficiencies)

The HIARC concluded that the toxicology database for MGK® Repellent 326 is adequate for FQPA considerations. The HIARC concluded that no additional safety factor is required to address traditional uncertainties (e.g., extrapolation from subchronic to chronic endpoints, use of a LOAEL due to lack of a NOAEL, incomplete database, etc).

3.2.2 Special FQPA Safety Factors

Since MGK Repellent 326 is not registered for use in/on foods and has no supported tolerances, the special FQPA safety factor is not applicable to risk assessments for this chemical. Although FQPA does not apply to this risk assessment, HED examined the toxicity and exposure databases to determine if any special concerns for infants and children exist. Based on this examination, HED has determined that this risk assessment is adequately protective of all population subgroups, including infants and children.

3.3 Dose Response Assessment

Doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 4.

Table 4. Toxicological Dose and Endpoints for MGK® Repellent 326 for Use in Human Risk Assessment

Exposure Scenario	Dose (mg/kg/day)	Special FQPA Safety Factor and Level of Concern	Endpoint for Risk Assessment
Dietary Risk Assessments			
Acute all populations	Not Applicable		
Chronic all populations	Not Applicable		
Non-Dietary Risk Assessments			
Incidental Oral Short-Term (1 - 30 Days)	NOAEL= 65	**FQPA SF = N/A** **LOC for MOE** = 100	**2-Gen. Repro. Study - Rat** LOAEL = 250 mg/kg/day based on decreased pup body weight on lactation day 21.
Incidental Oral Intermediate-Term (1 - 6 Months)	NOAEL= 65	**FQPA SF = N/A** **LOC for MOE** = 100	**2-Gen. Repro. Study - Rat** LOAEL = 250 mg/kg/day based on decreased pup body weight on lactation day 21.
Dermal * Short-Term (1 - 30 days)	Oral NOAEL= 65	**FQPA SF = N/A** **LOC for MOE** = 100	**2-Gen. Repro. Study - Rat** LOAEL = 250 mg/kg/day based on decreased pup body weight on lactation day 21.
Dermal * Intermediate-Term (1 - 6 Months)	Oral NOAEL= 65	**FQPA SF = N/A** **LOC for MOE** = 100	**2-Gen. Repro. Study - Rat** LOAEL = 250 mg/kg/day based on decreased body weight on lactation day 21.
Dermal * Long-Term (> 6 Months)	Not required based on use pattern		
Inhalation Short-Term (1 - 30 days)	Inhalation NOAEL= 60	**FQPA SF = N/A** **LOC for MOE** = 100	**90 - day Inhalation - Rat** LOAEL = 60 mg/kg/day based on lack of toxicity at highest dose tested
Inhalation Intermediate-Term (1 - 6 Months)	Inhalation NOAEL= 60	**FQPA SF = N/A** **LOC for MOE** = 100	**90 - day Inhalation - Rat** LOAEL = 60 mg/kg/day based on lack of toxicity at highest dose tested
Inhalation Long-Term (>6 Months)	Not required based on use pattern		
Cancer	**Classification:** B2: probable human carcinogen based on multiple malignant and benign tumors in the rat and in the mouse. **Q1*** = 1.6×10^{-3} $(mg/kg/day)^{-1}$		

* Since the dermal exposure endpoints were selected from oral toxicity studies, a dermal absorption factor is required to convert the oral dose to an equivalent dermal dose for the risk assessment.

3.3.1 Dietary Exposure Endpoints

There are no registered uses involving direct application of MGK® Repellent 326 to agricultural crops or to livestock. Therefore dietary exposure endpoints were not required for the assessment. HED recommends revocation of tolerances for the following commodities for which uses have been deleted from MGK® Repellent 326 product labels; meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep, and milk (40 CFR §180.143).

3.3.2 Residential Exposure Endpoints

3.3.1.1 Incidental Oral Exposure - Short & Intermediate Term Exposure Duration

The HIARC selected a dose and endpoint of 65 mg/kg/day from a two generation reproduction study in the rat based on decreased pup body weight occurring on lactation days 14-21 at a LOAEL of 250 mg/kg/day. Dose and endpoint was not required for the chronic exposure scenario since the use pattern (seasonal) does not indicate the potential for long term exposure.

3.3.1.2 Dermal Exposure - Short and Intermediate Term Exposure Duration

The HIARC selected a dose and endpoint of 65 mg/kg/day from a two generation reproduction study in the rat based on decreased pup body weight occurring on lactation days 14-21 at a LOAEL of 250 mg/kg/day. Dose and endpoint was not selected for the chronic exposure scenario because the use pattern (seasonal) does not indicate the potential for long term exposure and because MGK® Repellent 326 has a short half-life.

3.3.1.3 Dermal Absorption

Since the dermal exposure endpoints were selected from oral toxicity studies, a dermal absorption factor is required to convert the oral dose to an equivalent dermal dose for the risk assessment. The HIARC reviewed three dermal absorption studies conducted on human volunteers and one dermal absorption study conducted in rats. Of the human studies, two were conducted using a formulation containing 1% MGK® Repellent 326, 17.5% DEET, and 5% MGK 264. The third human study was conducted with technical MGK® Repellent 326 (purity 99.7%). The rat study was also conducted using technical MGK® Repellent 326 (purity 99.5%). When all of these studies are considered, the human dermal absorption studies are likely to provide the most appropriate dermal absorption factor. Also, use of a composite formulation of 17% DEET, 5% MGK-264, and 1% MGK® Repellent 326 is reasonable as this formulation is representative of MGK® Repellent 326-containing repellents sold for personal use based on currently active labels. DEET and MGK® Repellent 326 are the active ingredients and MGK-264 is used to

enhance the effectiveness of the repellent. There are no repellent end-use products in which MGK-326 is the sole active ingredient. Therefore, HIARC selected a dermal absorption factor (DAF) of 5% based on results of the two human studies with 1% MGK® Repellent 326 formulations (which indicated DAFs of 3.4 and 4.7%).

3.3.1.4 Inhalation Exposure - Short and Intermediate Term Exposure Durations

The HIARC selected a dose for inhalation risk assessment of 60 mg/kg from a 90 day inhalation rat toxicity study based on lack of toxicity at this dose. Dose and endpoint was not selected for the chronic exposure scenario because the use pattern (seasonal) does not indicate the potential for long term exposure and because MGK® Repellent 326 has a short half-life.

3.3.1.5 Common Toxicological Endpoints for Aggregate Risk Assessment

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal, and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated because the endpoint of concern (decrease in pup body weight) is the same for all three routes of exposure.

3.3.1.6 Classification of Carcinogenic Potential

The HED Carcinogenicity Peer Review Committee (CPRC) classified MGK® Repellent 326 as Group B2 - probable human carcinogen with an inadequate evidence in humans (HED memo July 21, 1993). This decision was based on the finding of multiple malignant and benign tumors in the rat and in the mouse. A Q_1^* based on liver adenomas, carcinomas and combined adenomas/carcinomas in rats was derived to be 1.6×10^{-3} $(mg/kg/day)^{-1}$ in human equivalents for the male rat and 8.2×10^{-4} $(mg/kg/day)^{-1}$ in human equivalents for the female rat. The registrant rebutted this classification and requested a second peer review of the carcinogenicity data based on a re-read of the histological slides by a consultant pathologist. However, for the reconsideration of the previous CPRC cancer classification, the revised pathology diagnosis should be the consensus of a pathology peer review group similar to that employed by the NTP according to Pesticide Regulation (PR) Notice 94-5 dated August 24, 1994. There is no record that such a pathology peer review group had been convened. Because HED has not received additional data from the registrant to allow for a re-evaluation the cancer classification, HED will not revisit this issue at this time. However, should additional data be submitted in the future, HED may revisit the cancer classification.

3.4 Endocrine Disruptor Effects

Available toxicity data suggest that there is no evidence of endocrine disruption following exposure to MGK® Repellent 326. EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA, and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, MGK® Repellent 326 may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

According to data provided by the registrant, repellent products containing MGK® Repellent 326 are used primarily in animal health products such as sprays for cats, dogs and horses (greater than 60% of total U.S. sales). Personal use repellents for application directly to humans account for approximately 40% of total U.S. sales. During the year 2002, 24,702 pounds of a.i. were produced and sold, of which 38% was sold to customers with pesticide labels for use as "personal insect repellents," 54% for use on horses, and 8% for use on dogs and cats (Use Closure Memo, T. Spears, 1/17/03). Additional usage information for human personal use repellents is provided in the survey study entitled, *Human Use and Exposure To Insect Repellents Containing DEET, Boomsma, J.C., and Parthasathy,* (1990, MRID 41968001). According to the DEET study, approximately 30% of the U.S. population use a DEET-containing insect repellent (which would include repellents containing MGK® Repellent 326) to repel biting insects. DEET repellent frequency usage across all product categories is approximately 7.5 times during the months of June and July (the time period in which the survey data were collected). Syndicated market data for 1990 show that the most commonly used insect repellents containing DEET are aerosols (71.9%), followed by pump sprays (15%), liquids (6%), lotions/creams (1.4%, roll-ons/sticks (0.7%) and towlettes, (0.2%). The amount of MGK® Repellent 326 in currently registered human personal use products ranges from 1 to 4%. The majority (approximately 90%) of human products contain 2.5% or less of the active ingredient (a.i.) MGK® Repellent 326. Two products contain a higher percentage a.i. (3 & 4%). The amount of MGK® Repellent 326 in animal products ranges from 0.1 to 5% with the majority of products containing 1% or less.

4.2 Dietary Exposure

There are no registered uses involving direct application of MGK® Repellent 326 to agricultural crops or to livestock.

4.3 Drinking Water Exposure

The only market niche for products containing this active ingredient are as personal and companion animal insect repellents. OPP's Environmental Fate and Effects Division (EFED) assumes that the amount from the product that is washed off the human body which could contaminate drinking water is negligible. Regarding the companion animal use, products used as surface sprays of premises (e.g., the interior of kennels, barns etc.) should not result in contamination of drinking water. Products used as pet dips would be discharged as waste water to septic systems or to sewage treatment plants. It is possible that Di-N-propyl

isocinchomeronate so disposed could pass on to surface or ground water if not fully degraded during treatment. However, EFED assumes the amount reaching drinking water from pet dip use would be negligible. (H. Craven, Memo on Drinking Water Concentrations, 11/22/02)

4.4 Residential Exposure/Risk Assessment

A regulatory review of residential exposure to MGK® Repellent 326 was conducted for the RED because there is residential exposure and potential risk due to direct application of insect repellents containing MGK® Repellent 326 to humans and pets. (D289351, D. Jaquith, 4/7/03). These repellent products may be applied as lotions, sprays, roll-on sticks, shampoos (for animals only) and towelettes. The products are applied on an as needed basis. It is likely that direct application to human skin would result in exposures to adults and children that exceed those from any animal applications. Therefore, the residential exposure assessment focused on direct application of MGK® Repellent 326 to humans.

The use frequency and quantity data used for the dermal exposure assessment were obtained from the 1990 survey study conducted for the insecticide repellent DEET and submitted by a joint group of registrants, the DEET Joint Venture/Chemical Specialties Manufacturers Association (MRID 41968001). A review of the DEET survey by OPP's Biological and Economics Analysis Division (BEAD) indicated that the survey data were acceptable for use in estimating consumer exposures to insect repellents containing DEET and MGK® Repellent 326 (Electronic correspondence, S. Smearman, 11/6/02). BEAD's review of the 1990 DEET survey included an analysis of the response to the survey, a comparison of data provided to pesticide usage information, and a determination on whether the survey was biased.

BEAD estimated that there are about 100 million households in the country. The survey was sent to 8,000 households. The "general population sample" (total individuals) consisted of a base of 12,224 individuals (not households). Based on an average of 3 members per household, there was an approximate 50% response rate for the survey (12,000 individuals/3 persons per household = 4000 households). BEAD concluded that, in general, the population surveyed was low but the response rate to the survey appeared to be good. Regarding pesticide usage information, BEAD found that the usage estimates provided in the survey were in line with national estimates and there was not much of a difference between the survey reported total usage and BEAD's proprietary data reported usage. Finally, BEAD concluded that there did not appear to be any obvious sources of bias in the survey. HED believes that the DEET survey study provides the most definitive data currently available for estimating exposures to MGK® Repellent 326 from use of insect repellant products.

Based on the DEET survey data, repellent products containing DEET and MGK® Repellent 326 were used an average of 7.5 times during the months of June and July, the time period in which the survey information was gathered. Syndicated market data for 1989-1990 shows that approximately 55-60% of yearly insect repellent sales occur during the months of June and July. Based on frequency of application data, only short and intermediate term exposures were assessed for non-cancer risks. The data on repellent frequency of use provided in the DEET survey were also used to estimate lifetime exposure for cancer risk estimates.

4.4.1 Exposure Assumptions

4.4.1.1 Dermal Exposure Assumptions

- Average body weights (NAFTA recommended):
  Adult Male - 77 kg
  Adult Female - 62 kg
  Child 12 and under - 25 kg (average weight of kids $\leq$ 12)
  Child 13-17 - 56 kg (average weight of kids 13 - 17)

  Note: The body weights and age ranges used for this assessment correspond to the age groupings for which exposure data were provided in the DEET survey.
- Mean amount of product applied to skin & clothing per application (DEET Survey):
  Adult Male - 5.2 g
  Adult Female - 4.3 g
  Child 12 years and under - 4.8 g
  Child 13 to17 years - 5.2 g
- Concentration of MGK® Repellent 326 in a product formulation intended for human application is 2.5%. Given that the large majority of products contain 2.5% or less a.i., HED believes this is a reasonable high-end estimate
- Oral NOAEL is 65 mg/kg/day
- Dermal Absorption of MGK® Repellent 326 is 5%

4.4.1.2 Incidental Oral Exposure Assumptions

Assumptions for incidental oral exposure are based on a conservative method for estimating potential exposure of children from a topical application of an insect repellent developed by HED for the KBR 3023 Exposure Assessment (S. Weiss, D269916, 10/24/00).

- Average body weight for toddlers 1-3 is 15 kg (NAFTA recommended)
- Oral NOAEL is 65 mg/kg/day

- Both hands of a child are covered with product at a conservative rate of 1 mg formulation/cm^2. Concentration of MGK® Repellent 326 in a formulation intended for human application is 2.5%
- Each single oral exposure event involves the child placing the palmar surface of 3 fingers of one hand into their mouth
- A saliva extraction factor of 0.5 is used to determine the quantity of product ingested

4.4.1.3 Inhalation Exposure Assumptions

- All MGK® Repellent 326 labels prohibit spraying of the face
- Inhalation exposure duration is extremely short (i.e., seconds)

4.4.1.4 Cancer Risk Exposure Assumptions

- Average adult body weight is 70 kg (NAFTA recommended)
- $Q_1^* = 1.6 \times 10^{-3}$
- Exposure duration is for the entire lifetime (i.e., 70 years)
- Persons are exposed for 12.5 days per year based on DEET survey data. This is based survey data indicating that MGK® Repellent 326 is used an average of 7.5 times (i.e., days) during June and July and that 60% of product sales occur in June and July.

$$\text{Use days/yr} = \frac{\text{\# Applications in June \& July}}{\text{Percent of sales in June and July}} = \frac{7.5}{0.6} = 12.5$$

4.4.2 Exposure and Risk Estimates

The target MOE is 100 for the inhalation, dermal, and incidental oral routes for the residential risk assessment. Results of the residential exposure assessment are presented in Table 5. The MOEs estimated for the residential exposure scenarios assessed showed no risks of concern (i.e. all MOEs were > 100). Estimated cancer risk for residential exposure to MGK® Repellent 326 is 7×10^{-6}. OPP's cancer level of concern for residential exposure is 1×10^{-6}. Therefore, MGK® Repellent 326 may present potential cancer risks of concern from residential exposure.

4.4.2.1 Dermal Exposure and Risk

The MOEs estimated for the dermal exposure route showed no risks of concern with MOEs ranging from 270 to 770. Dermal exposure estimates are presented in Table 5.

Table 5. Residential Assessment of Use of MGK® Repellent 326 - Dermal Exposure							
Age Group	Oral NOAEL (mg/kg/day)	Applied Dose (mg/kg/day)	Dermal Absorption (%)	Body Weight (kg)	Daily Dose (mg/kg/day)[1]	MOE [1]	Target MOE
Child ≤ 12 years	65	120	5	25	0.24	270	100
Child 13-17 years	65	130	5	56	0.12	565	100
Adult Female	65	107	5	62	0.09	750	100
Adult Male	65	130	5	77	0.08	770	100

$$\text{MOE} = \frac{\text{Oral NOAEL(mg/kg/day)}}{\text{daily dermal dose (mg/kg/day)}}$$

where:

Daily Dermal Dose = (applied dose (mg) * dermal absorption factor) ÷ body weight (kg)
Applied Dose = Applied Dose of Repellant Product from DEEM Survey x % MGK-326 in Product (2.5%)
Dermal Absorption Factor = 5%

[1] Assumes one application per day

Residential exposure calculations presented in Table 5 are based on the assumption that MGK® Repellent 326 is applied once per day. An assessment of the number of applications per day which may be applied without exceeding the target MOE of 100 is provided in Table 6. Based on this assessment, children 12 years and younger can use 3 applications, children 13-17 can use 6 applications, and adults can use 8 applications per day without exceeding the target MOE.

Table 6. Residential Assessment of Use of MGK® Repellent 326 - Dermal Exposure							
Age Group	Oral NOAEL (mg/kg/day)	Applied Dose (mg/kg/day)	Dermal Absorption (%)	Body Weight (kg)	Daily Dose (mg/kg/day)	No. Applications/day	MOE
Child ≤ 12 yrs	65	325	5	25	0.65	3	100
Child 13 -17 yrs	65	735	5	56	0.65	6	100
Adult Female	65	806	5	62	0.65	8	100
Adult Male	65	1001	5	77	0.65	8	100

4.4.2.2 Incidental Oral Exposure and Risk

The MOE for incidental oral ingestion of MGK® Repellent 326 via hand to mouth activity is 4100, well above the target MOE of 100. The MOE is calculated for directed application of repellent to a child's skin. It is likely that direct application to human skin would result in exposures that exceed those from transference from animal applications. The MOE calculation for this exposure route is as follows:

$$\text{Incidental Oral Exposure} = \frac{1\ \text{mg pdt/cm}^2 \times 0.025\ \text{mg MGK326/mg pdt} \times 20\ \text{cm}^2 \times 0.5\ \text{(saliva)}}{15\ \text{kg}}$$

$$\text{MOE} = \frac{\text{Oral NOAEL (mg/kg/day)}}{}$$

$$\text{Incidental Oral Exposure} = 0.016 \text{ mg/kg/application}$$

(mg/kg/application)

$$\text{MOE} = 4100$$

4.4.2.3 Inhalation Exposure and Risk

Inhalation exposure is expected to be negligible compared to dermal exposure, particularly when applications are made using non-aerosol products. The vapor pressure of MGK® Repellent 326 is very low (4.92×10^{-7}) so there would be virtually no vapor generated by non-aerosol products. All MGK® Repellent 326 labels prohibit spraying of the face. Additionally, inhalation exposure duration from aerosol application is expected to be extremely short (i.e., typically a few seconds). Based on these considerations, inhalation exposure to MGK® Repellent 326 would not significantly affect exposures calculated for the dermal exposure route.

4.4.2.4 Aggregate Dermal and Incidental Oral Exposure and Risk

The aggregate risk is the estimated risk from combined risks from short and intermediate term dermal and incidental oral exposures. The toxicity endpoints selected for these exposure routes may be aggregated because the endpoint of concern is the same for both routes of exposure. The inhalation pathway shares a common endpoint, however inhalation risks are negligible. Aggregate risk is estimated for the child exposure scenario only since the child may be exposed via both the incidental oral and dermal pathways while the adult exposure is from the dermal route only. The aggregate MOE for the child is calculated by adding exposure estimates from the oral and dermal pathways using the formula below. The aggregate MOE for the child is 250.

$$\text{MOE Aggregate}_{\text{CHILD}} = \frac{1}{\frac{1}{\text{MOE}_{\text{DERMAL}}} + \frac{1}{\text{MOE}_{\text{ORAL}}}} = \frac{1}{\frac{1}{270} + \frac{1}{4100}}$$

$$\text{MOE} = 250$$

4.4.2.5 Cancer Exposure & Risk

Estimated cancer risk for MGK® Repellent 326 is 5×10^{-6}. In general, the Agency is concerned if cancer risk estimates exceed 1×10^{-6} Therefore, MGK® Repellent 326 may present potential cancer risks of concern from residential exposure. The cancer risk estimate is calculated as follows:

$$\text{Annual Dermal Exposure - Adult (mg/kg/day)} = \frac{12.5 \text{ applications/yr}}{365 \text{ days/yr}} \times 0.09 \text{ mg/kg/application}$$

Annual Dermal Exposure = 0.003 mg/kg/day

$Q_1^* = 1.6 \times 10^{-3}$

Cancer Risk = Annual Dermal Exposure x Q_1^*

Cancer Risk** = 5×10^{-6}

** estimate assumes that MGK® Repellent 326 Repellent will be used every year over a 70-year lifetime

4.5 Incident Report Summary

No illness cases have been reported due to exposure solely to MGK® Repellent 326. (J. Blondell, personal correspondence 11/14/02).

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

5.1 Aggregate Risk

Since there is no potential for concurrent exposure via the food, water and residential pathways, an aggregate assessment of risk from these combined pathways was not conducted. This assessment estimated exposure and risk for dermal exposure from direct application of MGK® Repellent 326 to human skin, incidental oral exposure of children from hand to mouth activity after topical application, and inhalation exposure from use of repellent sprays. Aggregate risk from different residential exposure pathways is estimated for the child exposure scenario only since the child may be exposed via both the incidental oral and dermal pathways while the adult exposure is from the dermal route only. The aggregate MOE for the child is calculated by adding exposure estimates from the oral and dermal pathways. The aggregate MOE for the child is 250.

5.2 Risk Characterization

The target Margin of Exposure (MOE) is 100 for all residential routes of exposure. The MOEs estimated for all of the residential exposure scenarios evaluated showed no risks of concern (i.e. all MOEs were > 100). Inhalation exposure is expected to be negligible based on manner and frequency of application and physical property data. An assessment of the number of applications per day which may be applied without exceeding the target MOE of 100 indicates that children 12 years and younger can use 3 applications, children 13-17 can use 6 applications, and adults can use 8 applications per day without exceeding the target MOE. The Q_1^* for the cancer risk estimate is 1.6×10^{-3} mg/kg/day. The estimated cancer risk for residential exposure to MGK® Repellent 326 is 5×10^{-6}. In general, the Agency is concerned if cancer risk estimates exceed 1×10^{-6} Therefore, MGK® Repellent 326 may present potential cancer risks of concern from residential exposure.

Estimates of daily and annual amounts of MGK® Repellent 326 applied were based on amount of repellent product applied to skin and clothing, and should therefore be considered conservative estimates. For the cancer risk estimate, the assumption that individuals are exposed annually for a lifetime (i.e., 70 years) should also be considered conservative. It is also important to note that the Q_1^* $(mg/kg/day)^{-1}$ is an estimate of the upper bound on risk. Alternatively, the assumption that MGK® Repellent 326 is applied seasonally, the majority of usage occurs in June and July, and a typical annual application rate is one application per day for 12.5 days may underestimate exposure in some situations. Under certain circumstances, applications may be more frequent and use periods longer, e.g., for forest service personnel or other persons with outdoor occupations. Finally, HED believes that the DEET survey study provides the most definitive data currently available for estimating exposures to MGK® Repellent 326 from use of insect repellants. It is important to note, however, that there are inherent uncertainties associated with use of survey data to determine rate and frequency of application of MGK® Repellent 326. The manner in which these uncertainties may effect exposure and risk estimates cannot be determined. In general, this assessment can be characterized as providing a conservative estimate of risk from exposure to MGK® Repellent 326.

6.0 CUMULATIVE RISK

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this assessment for MGK® Repellent 326 because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of MGK® Repellent 326. On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether MGK® Repellent 326 shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for MGK® Repellent 326 need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with MGK® Repellent 326, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at: http://www. cumulative_guidance.pdf epa.gov/ pesticides/trac/science/. In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity" (64 FR 5795-5796, February 5, 1999).

7.0 DATA NEEDS

7.1 Product and Residue Chemistry Data Requirements

All pertinent chemistry data requirements are satisfied except Guidelines 830.7050 (UV/Visible Absorption), 830.1700 (Preliminary Analysis), 830.1750 (Certified Limits) and 830.1800 (Enforcement Analytical Method). Most of the necessary data has been submitted, however, and HED has no objections to the reregistration of MGK® Repellent 326 based on product chemistry requirements, provided that the registrant submits the outstanding data.

7.2 Toxicology Data Requirements

All required toxicological data have been submitted.